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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
DISCUSSION	7
AUTHORS' CONCLUSIONS	7
ACKNOWLEDGEMENTS	7
REFERENCES	8
CHARACTERISTICS OF STUDIES	10
APPENDICES	11
WHAT'S NEW	13
HISTORY	14
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14
INDEX TERMS	14

[Intervention Review]

Treatment for amphetamine psychosis

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ABSTRACT

Background

Chronic amphetamine users may have experience of paranoia and hallucination. It has long been believed that dopamine antagonists, such as chlorpromazine, haloperidol, and thioridazine, are effective for the treatment of amphetamine psychosis.

Objectives

To evaluate risks, benefits, costs of treatments for amphetamine psychosis.

Search methods

MEDLINE (1966-2007), EMBASE (1980-2007), CINAHL (1982-2007), PsychINFO (1806-2007), CENTRAL (Cochrane Library 2008 issue 1), references of obtained articles.

Selection criteria

All randomised controlled and clinical trials (RCTs, CCTs) evaluating treatments (alone or combined) for people with amphetamine psychosis

Data collection and analysis

Two authors evaluated and extracted the data independently. Dichotomous data were extracted on an intention-to-treat basis in which the dropouts were assigned as participants with the worst outcomes. The Relative Risk (RR) with the 95% confidence interval (95% CI) was used to assess the dichotomous data. The Weighted Mean Difference (WMD) with 95% CI was used to assess the continuous data.

Main results

The comprehensive searches found one randomised controlled trial of treatment for amphetamine psychosis meeting the criteria for considering studies. The study involved 58 participants and compared the efficacy and tolerability of two antipsychotic drugs, olanzapine (a newer antipsychotic) and haloperidol (a commonly used antipsychotic medication used as a control condition), in treating amphetamine-induced psychosis. The results show that both olanzapine and haloperidol at clinically relevant doses were efficacious in resolving psychotic symptoms, with the olanzapine condition showing significantly greater safety and tolerability than the haloperidol control as measured by frequency and severity of extrapyramidal symptoms.

Authors' conclusions

Only one RCT of treatment for amphetamine psychosis has been published. Outcomes from this trial indicate that antipsychotic medications effectively reduce symptoms of amphetamine psychosis, the newer generation and more expensive antipsychotic medication, olanzapine, demonstrates significantly better tolerability than the more affordable and commonly used medication, haloperidol.

There are other two studies that did not meet the inclusion criteria for this review. The results of these two studies show that agitation and some psychotic symptoms may be abated within an hour after antipsychotic injection.

Whether this limited evidence can be applied for amphetamine psychotic patients is not yet known.

The medications that should be further investigate are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and the prevalence of relapse to psychosis in the presence of amphetamine, are also crucial for advising the development of study designs appropriate for further treatment studies of amphetamine psychosis.

PLAIN LANGUAGE SUMMARY

Treatment for amphetamine psychosis

A minority of individuals who use amphetamines develop full-blown psychosis requiring care at emergency departments or psychiatric hospitals. In such cases, symptoms of amphetamine psychosis commonly include paranoid and persecutory delusions as well as auditory and visual hallucinations in the presence of extreme agitation. More common (about 18%) is for frequent amphetamine users to report psychotic symptoms that are sub-clinical and that do not require high-intensity intervention. Clinical reports suggest the development of amphetamine psychosis and of sub-clinical psychosis symptoms is related to the individual's lifetime history of amphetamine use, i.e., cumulative quantity and frequency of exposure to amphetamines. In one of the only randomised trials of antipsychotic medications for treating amphetamine psychosis, Leelahanaj (2005) reported that olanzapine and haloperidol delivered at clinically relevant doses both showed similar efficacy in resolving psychotic symptoms (93% and 79%, respectively), with olanzapine showing significantly greater safety and tolerability than haloperidol as measured by frequency and severity of extrapyramidal symptoms. These outcomes are consistent with treatments for schizophrenia indicating equivalent efficacy between atypical anti-psychotics and conventional anti-psychotics, mostly haloperidol with older drugs causing more severe side effects (Leucht 1999). While anti-psychotic medications demonstrate efficacy in providing short-term relief when a heavy user of amphetamines experiences psychosis, there is no evidence to guide decisions regarding long-term clinical care using these medications for preventing relapse to psychosis.

BACKGROUND

It is generally agreed that enhancing the release of dopamine in the nucleus accumbens is of major importance in mediating amphetamines reinforcing and psychomotor stimulant effects (Altman 1996). While other types of stimulants such as cocaine, which act through storage pools of catecholamines, amphetamines increase the release of newly synthesized norepinephrine and dopamine (Ellinwood 1977). The mechanism underlying psychosis following heavy use of amphetamines is integrally linked to the neurobiology of the stimulants. The amphetamines accumulate at high levels in brain following ingestion due to highly lipophilic properties (Fowler 2007). Once ingested, users experience immediate effects that include profound feelings of euphoria and well being, sharpening of attention, and increasing levels of energy (Meredith 2005). There is a growing literature that addresses specific initial (acute) and long-term (chronic) effects to the neurobiology of amphetamine abuse. But a general understanding of the neurological bases of methamphetamine, particularly at acute, high doses is likely related to observed reductions in the number of dopamine transporters in striatum in humans (Volkow 2001). Methamphetamine use also leads to down-regulation of D2 dopamine receptors in the striatum (Chang 2006) and areas in the nucleus accumbens and anterior cingulate cortex (Paulus 2002; Leland 2008). There is some evidence that a neurobiological consequence of methamphetamine abuse involves changes in brain volume (Jernigan 2005), a finding that is consistent with volumetric increases in laboratory animals exposed to methamphetamine. Methamphetamine is toxic to 5-HT terminals in forebrain regions (Armstrong 2004), which also may contribute to protracted neurobiological changes, cognitive deficits and psychotic symptoms commonly observed in methamphetamine abusers. The duration and magnitude of these neurobiological effects are dose dependent. Likelihood for recovery from abuse of amphetamines is also linked to severity of use, with those individuals with less severe amphetamine use disorders more likely to achieve sustained abstinence than those with more severe amphetamine use disorders.

It is difficult to pinpoint, exactly, the prevalence of amphetamine-induced psychosis, either locally or worldwide. Existing prevalence estimates are derived from Emergency Department records (where patients experiencing severe psychosis symptoms present) and surveys of active amphetamine users. Approximately 1.2% of 13,125 Emergency Department admissions to a Perth Australia tertiary care hospital over 3 months in 2005 involved amphetamine use (Gray 2007). The most common presentation involved psychiatric problems that included amphetamine-induced delirium ($n=31$; 19.9%) and acute psychosis ($n=19$; 12.2%) and of these, 25 patients (16%) had prior episodes of amphetamine-induced psychosis, which compared to 8.3% ($n=13$) who had known diagnoses of schizophrenia. In psychiatric facilities in Thailand, approximately 10% of admissions are attributed to methamphetamine-related psychosis (Farrell 2002).

Surveys of current users of amphetamines indicate that psychotic symptoms are common and are directly associated with extent of use of the drug. In one survey of 309 actively-using individuals in Sydney Australia (McKetin 2006) 13% screened positive for acute psychosis in the past year and 23% reported "clinically significant suspiciousness, unusual thought content or hallucinations, with hallucinations and suspiciousness more common than delusional

thoughts." When excluding participants with schizophrenia or other psychotic disorders, prevalence of clinically significant psychosis symptoms was 18%. In 180 methamphetamine-using youth in Canada, similar associations were observed between reported levels of use and auditory hallucinations (Martin 2006). Thus, the epidemiology of the disorder indicates that patients with symptoms of acute psychosis due to amphetamine use present to Emergency Departments and Psychiatric Units at a low rate compared to the census of all patients and that significant psychotic symptoms are common to users with more extensive and severe amphetamine use patterns.

The clinical picture of those affected by amphetamine psychosis is better described in the literature. Among those who experience amphetamine psychosis symptoms, resolution usually occurs with abstinence, though the resolution may be incomplete, increasing risks for drug relapse (Ujike 2004). Psychotic symptoms due to amphetamine abuse generally resolve with medications used to treat schizophrenia (Leucht 1999) for those seen in emergency departments and psychiatric units, including antipsychotic or benzodiazepine medications. Similarities in clinical presentation between those with amphetamine psychosis and with schizophrenia complicate understanding the underlying mechanisms regarding amphetamine psychoses: psychotic symptoms of individuals with amphetamine psychosis may be due exclusively to heavy use of the drug or heavy use of the drug may exacerbate an underlying vulnerability to schizophrenia. Empirically derived information could positively impact the ongoing health of patients who experience amphetamine psychosis, while controlled evaluation of antipsychotic medications used following resolution of psychotic symptoms has high public health significance given the potential for side effects using neuroleptic treatment.

Much of the study on amphetamine psychosis is based on work from Japan. In one study, onset of amphetamine psychosis was found to commence between 4 months to more than 4 years of amphetamine use (Sato 1992). A contrasting study reported onset of amphetamine psychosis after between 1.5 and 2 years of multiple daily injections each consisting of 10mg to 60mg of methamphetamine (Yui 2002). Clinically, acute amphetamine psychosis is virtually indistinguishable from that of acute schizophrenia (Sato 1992), though there are indications the two disorders may be linked genetically. Relatives of methamphetamine-users with a lifetime history of amphetamine psychosis are 5 times more likely to have schizophrenia than methamphetamine-users without a history of methamphetamine psychosis (Chen 2005). Biomarkers for the two conditions are also similar. Patients with schizophrenia and with amphetamine induced psychosis show significantly increased peripheral plasma levels of norepinephrine than levels in methamphetamine users who do not have psychosis and non-methamphetamine-using controls (Yui 1997, Yui 2000). In both conditions, patients appear for treatment with psychiatric manifestations that include hallucinations, delusions of reference and intense suspiciousness and paranoia in the setting of agitation and clear consciousness (Dore 2006; Srisurapanont 2003). In amphetamine psychosis, persecutory delusions are most frequent, followed by auditory and visual hallucinations. A minority of patients experience negative symptoms (Srisurapanont 2003). The similarities shared by amphetamine psychosis and schizophrenia, both clinically and metabolically, raise questions of whether amphetamine psychosis

is a unique presentation or if drug-induced symptoms represent an underlying vulnerability to schizophrenia. Distinguishing between these disorders is most often determined by quick resolution of symptoms in amphetamine psychosis, which is not a likely outcome of schizophrenia (Mclver 2006).

While the mechanisms of the two disorders may differ, the management, treatment, and treatment responses of acute amphetamine psychosis are much like that of acute schizophrenia; administration of neuroleptics produces similar responses (Fujii 2002). Patients with acute amphetamine psychosis seen in the emergency departments are typically treated with antipsychotics and/or benzodiazepine medications to reduce symptoms of psychosis, to minimize side effects and to contain behavioral agitation (Mclver 2006). There is a suggestion that neuroleptics may help to prevent recurrence of amphetamine psychosis (Sweeting 2005), though this implication is not based on controlled data. About 5-15% of the users who develop an amphetamine psychosis fail to recover completely (Hofmann 1983). In one report (Akiyama 2006) 31 of 32 methamphetamine-dependent women incarcerated in Japan and treated using antipsychotic medications experienced psychosis symptoms 5 to 31 months after their last methamphetamine injection. Of these, 9 (29%) experienced full psychosis relapses.

Chronic amphetamine psychosis is even more enigmatic and disturbing. In Japanese reports, about "82 percent of patients with of amphetamine psychosis recover from the paranoid psychotic state within a month after withdrawal (Sato 1992)." The psychotic state recurs promptly with subsequent use, however, even a small dose, suggesting an amphetamine-induced mechanism may trigger such symptoms. Exposure to psychosocial stressors can also exacerbate the risks for relapse to amphetamine psychosis (Yui 2002), in some cases without actual re-exposure to the drug.

No medication has been approved for the treatment of amphetamine dependence, although anti-psychotics are used commonly in the management of amphetamine psychosis. This is based on experience with schizophrenia despite little systematic study on their use in the treatment of acute amphetamine psychosis and chronic, recurrent amphetamine psychosis. There is no database to guide use of these medications, particularly relative to the time course of amphetamine psychosis, its persistence and relapse and potential for emergence of late effects, side effects, and complications to the medications. Questions relating to these issues are unsettling for clinicians due to risks for stereotypes and movement disorders. In addition, the use of ascorbic acid can accelerate the renal elimination of amphetamines (Beckett 1965).

This systematic review relevant to the treatment of amphetamine psychosis is intended to guide those providing evidence-based medical services to patients with amphetamine-induced psychosis. Although there are a variety of amphetamines and amphetamine derivatives, the word "amphetamines" in this review stands for amphetamine, dextroamphetamine, and methamphetamine.

OBJECTIVES

To search and determine risks, benefits, and costs of a variety of treatments for amphetamine psychosis.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs) and clinical controlled trials (CCTs) were included.

Types of participants

People with amphetamine psychosis, diagnosed by any set of criteria. The study carried out in both amphetamine psychotic patients and other substance-induced psychotic patients would be included only if:

1. The data of amphetamine psychotic patients were reported separately, or
2. More than half of the participants were amphetamine psychotic patients

However, a sensitivity analysis was conducted to determine the appropriateness of including the data obtained from a study in which most (50%-75%) participants were amphetamine psychotic patients (see Methods of the review). For a study in which almost all (more than 75%) participants were amphetamine psychotic patients, its data were included as those of study in which all participants were amphetamine psychotic patients.

Since acute and chronic amphetamine psychoses may be different from each other in the respects of pathophysiology, clinical features, response to treatment, course of illness, and prognosis.

People with amphetamine psychosis were divided into: i) acute psychotic patients - their psychotic symptoms persist for 4 weeks (or 1 month) or less, and ii) chronic psychotic patients - their psychotic symptoms persist for more than 4 weeks (or 1 month).

Types of interventions

1. Placebo,
2. Any kind of pharmacological treatment,
3. Any kind of psychosocial treatment, and
4. Any kind of combined pharmacological and psychosocial treatment.

Types of outcome measures

1. Number of people who response to treatment (as priori criteria),
2. Incidence of extrapyramidal side effects (EPSs), including acute dystonia, parkinsonism, and akathisia,
3. Incidence of use of antiparkinson drugs for treating EPSs
4. Discontinuation rate
5. Death.
6. Global status as measured by global psychiatric rating scales, e.g., Clinical Global Impression (CGI),
7. Psychotic symptoms as measured by psychotic rating scales, e.g., Brief Psychiatric Rating Scale (BPRS),
8. Side effects as measured by rating scales for positive symptoms
9. Duration of adherence to treatment.
10. Patient satisfaction e.g. type and number of adverse events and side effects experienced,
11. Functioning,

12. Health status or health-related quality of life, and
13. Economic outcomes.

All outcomes were reported for the short term (4 weeks or 1 month), medium term (more than 4 weeks or 1 month to 12 weeks or 3 months), and long term (more than 3 months). If any outcome was assessed more than once in a particular term, only the results of the longest duration in that term were considered.

Search methods for identification of studies

The search incorporated a number of methods to identify completed or ongoing studies.

Electronic searches

- We originally searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2000, Issue 4), MEDLINE (January 1966 to December 2000) and EMBASE (January 1980 to December 2000).
- For this updated version we searched CENTRAL through to 2007, Issue 4 of *The Cochrane Library*, and MEDLINE, EMBASE, PsychInfo and CINAHL through to December 1, 2007. For details see [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#)

Searching other resources

We also searched:

- the reference lists of all relevant papers to identify further studies.
- some of the main electronic sources of ongoing trials (Current Controlled Trials - <http://www.controlled-trials.com/>, Clinical Trials.gov, [Trialsjournal.com](http://www.trialsjournal.com))
- conference proceedings likely to contain trials relevant to the review.

We contacted investigators seeking information about unpublished or incomplete trials.

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Data collection and analysis

Selection of Trial

In the original review, reports identified by the electronic searches were assessed for relevance. Two reviewers (MS & NJ) independently inspected all study citations identified by the electronic searches and full reports of the studies of agreed relevance were obtained. Where disputes arose the full reports were acquired for more detailed scrutiny. The reviewers (MS & NJ) then independently inspected all these full study reports.

For this update of the review, one author (UK) inspected the search hits by reading titles and abstracts. Each potentially relevant study located in the search was obtained in full text and assessed for inclusion independently by two authors (SS & UK). Discrepancies were resolved by discussion between the authors.

The corresponding author was contacted if information necessary for the review was not available in the reports.

Quality Assessment

In both the original and the updated reviews, the quality of methodology of each selected study was independently rated

by the authors using the Cochrane Collaboration Reviewer's Handbook ([Higgins 2006](#)). As above, discrepancies in ratings were resolved in discussions. The trial quality was based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment ([Schulz 1995](#)) and was defined as below:

- A. Low risk of bias (adequate allocation concealment),
- B. Moderate risk of bias (unclear allocation concealment),
- C. High risk of bias (inadequate allocation concealment), and
- D. No allocation concealment used.

Data Collection

Data were extracted independently onto data extraction forms. Again, if the disputes arose these were resolved either by discussion between the two reviewers or the correspondence author of the paper.

Data Synthesis

In conducting a meta-analysis, a fixed effect model, an analysis that ignores the between-study variation, can give a narrower confidence interval than a random effect model. It is generally agreed that the fixed effect model is valid as a test of significance of the overall null hypothesis (i.e. 'no effect in all studies'). A statistically significant result obtained by the use of this model indicated that there is an effect in at least one of the studies. Because of these advantages, the fixed effect model was used for the synthesis of a group of data with homogeneity. Although a random effect model can be applied for the synthesis of a group of data with significant heterogeneity, the results obtained by the synthesis of this group of data have to be interpreted with great caution. The reviewers, therefore, decided to disregard the groups of data with significant heterogeneity.

As high attrition rate would affect the study results, the studies with the attrition rate of 50% or higher of the total participants will be excluded.

Other than raw data (e.g. death), the outcomes derived from only valid scales will be included in the reviews. In this review, a valid scale means a scale that has been published in a scientific journal.

Dichotomous data: The Relative Risk (RR) with the 95% confidence interval (95% CI) was used. RR is the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

In addition, as a measure of efficacy, the number needed to treat (NNT) was also calculated. The reviewers extracted the dichotomous data on an intention-to-treat basis by applying the following guidelines to analyse data from included studies: (i) the analysis included all those who entered the trial; and (ii) the analysis maintained the study groups according to the original randomisation procedure. The reviewers assigned people lost to follow-up to the worst outcome.

Continuous data: The Weighted Mean Difference (WMD) with 95% CI was used. WMD is a method of meta-analysis used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The

weight given to each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan and CDSR, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

For the studies that the treatment and/or controlled groups were divided into subgroups because of the differences of concurrent treatment, the continuous data of the subgroups receiving more rigorous treatment, e.g., higher doses of drug treatment, more intensive psychotherapy, would be extracted.

Sensitivity Analysis

Sensitivity analysis is an analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

The reviewers examined whether the decision to include the data obtained from studies in which most (50%-75%) participants were amphetamine dependents or abusers, affected the results of the review. The sensitivity analyses were done by the inclusion and exclusion of the data obtained from these studies. If both analyses point to the same conclusion in the respect of significant heterogeneity of data, the meta-analyses including the data obtained from these studies were taken into consideration. Otherwise, the meta-analyses conducted by the exclusion of the data obtained from these studies were considered.

Test for Heterogeneity

Test of heterogeneity is important to check whether the results of studies are similar within each comparison. The reviewers checked whether differences between the results of trials were greater than could be expected by chance alone. This was done by looking at the graphical display of the results but also by using Chi square tests of heterogeneity. A p-value being less than 0.05 of a Chi-square test indicated the significant heterogeneity of a data set. The statistical methods for dealing with a data set with significant and non significant heterogeneity were described in 'Data synthesis'. In addition, the possibly causes leading to the significant heterogeneity of a data set were discussed.

RESULTS

Description of studies

Included studies

One study satisfied all the criteria to be included in the review (Leelahanj 2005). The study compared the efficacy and tolerability of olanzapine and haloperidol for the treatment of amphetamine-induced psychosis. The study included 58 amphetamine psychotic participants according to DSM-IV criteria, who were randomly assigned to either receive a dose range of 5-20 mg/day for 4 weeks of olanzapine (N=29) or a dose range of 5-20 mg/day for 4 weeks of haloperidol (N=29). Ninety-three percent of the sample were men, with a mean age of 22.7 years (SD=4.8). The average duration of amphetamine use prior to randomisation was 4.5 years (SD=2.1). The study was conducted in an outpatient setting.

Excluded studies

Seven studies (Baker 2006; Batki 2004; Breier 1999; Brown 2003; Chen 2005; Richards 1997; Srisurapanont 2003) did not meet the criteria for inclusion in this review. The grounds for exclusion were the following: two studies excluded for participant type not in the inclusion criteria (Baker 2006; Richards 1997); one study excluded for the type of intervention not in the inclusion criteria (Brown 2003); four studies excluded for objective and study design not in the inclusion criteria (Batki 2004; Breier 1999; Chen 2005; Srisurapanont 2003).

Risk of bias in included studies

One randomised controlled trial of treatment for amphetamine psychosis met the criteria to be included in the review (Leelahanj 2005). The study was double-blinded and reported using a simple randomisation but did not specify its allocation concealment approach. The methodological quality was not used as a criterion for inclusion.

Effects of interventions

Because only one study met the criteria to be included in this review (Leelahanj 2005), the results are presented narratively.

Number of people who responded to treatment

Treatment response was defined as having 40% or greater Brief Psychiatric Rating Scale (BPRS) total improvement from baseline to endpoint. Twenty-seven of 29 olanzapine patients and 23 of 27 haloperidol patients responded to treatment.

Discontinuation rate

Twenty-seven of the 29 olanzapine patients and 19 of 29 haloperidol patients completed the 4-week medication period. The two olanzapine patients that discontinued were due to noncompliance and lost to follow-up whereas the 10 haloperidol patients were due to extrapyramidal side effects.

Average score/change in global state

Participants in both olanzapine and haloperidol showed significant improvements on the Clinical Global Impression (CGI) scale from baseline to endpoint (paired t test, $p < 0.001$). Higher scores denote more severity. The average change in CGI score from baseline to endpoint was 3.3 and 3.1 for olanzapine and haloperidol, respectively. The standard deviations for this outcome could not be calculated based on the data available.

Average score/change in psychotic symptoms

Participants in both olanzapine and haloperidol showed significant improvements on the Brief Psychiatric Rating Scale (BPRS) scores from baseline to endpoint (paired t test, $p < 0.001$). The average change in BPRS scores from baseline to endpoint was 10.4 and 8.9 for olanzapine and haloperidol, respectively. The standard deviations for this outcome could not be calculated based on the data available.

Average score/change in extrapyramidal symptoms

Olanzapine showed no change in Simpson-Angus Scale (SAS) scores from baseline to endpoint (median=0.0, range 0.0). In contrast, haloperidol had a worsening effect as showed by the increased change in SAS score (median=0.2, range=0.0-3.1).

Olanzapine showed minimal change in Barnes Akathisia Scale (BAS) global scores from baseline to endpoint (median=0.0, range=-1.0-0.0), whereas haloperidol showed a worsening effect by the increased change in BAS score (median=0.0, range=-1.0-3.0).

Overall, olanzapine was significantly favoured over haloperidol as measured using changes in extrapyramidal symptoms, though the means and standard deviations for this outcome were not reported.

Patient satisfaction

The type and number of adverse events and or side effects experienced by participants were used as a measure of patient satisfaction. Among participants treated with olanzapine, adverse events included somnolence, headache, and skin rash. Among haloperidol treated participants, somnolence, insomnia, hypersalivation, hypertonia, dyskinesia, and extrapyramidal syndromes were reported. There was no difference in the number of adverse events experienced between these groups, except for extrapyramidal syndromes, which were reported only by haloperidol treated participants. A side effect of both olanzapine and haloperidol was weight gain, with olanzapine having significantly greater weight gain than haloperidol.

DISCUSSION

The evidence about the treatment for amphetamine psychosis is very limited. To our knowledge, there has been one randomised-controlled trial of treatment for amphetamine psychosis. The results of the trial show that both olanzapine and haloperidol at clinically relevant doses can be effective in the treating patients with amphetamine-induced psychosis. The mean doses recommended for olanzapine and haloperidol are 7.5 mg/day and 7.8mg/day, respectively. The results of the study also suggest that olanzapine may be a better treatment option than haloperidol in light of an inducing few to no extrapyramidal symptoms, although the medication costs substantially more than haloperidol. The study has a small sample size (n=58), thus the findings should be interpreted with cautions.

Although they do not meet the criteria to be included in the review, the results of two other studies are worth mentioning. The results of an open study including eight amphetamine psychotic patients show that the symptoms of excitement and paranoid ideation are significantly decreased within 60 minutes of haloperidol intramuscular administration (Angrist 1974). The results of a randomised-controlled trial in 146 acutely agitated methamphetamine users show that droperidol, a butyrophenone, can sedate the patients significantly faster than lorazepam at 10, 15, 30 and 60 minutes after the intravenous administration (Richards 1997).

Because an antipsychotic injection demonstrated its effectiveness for agitation and some psychotic symptoms occurring in amphetamine users, its risks and benefits should be further investigated in amphetamine psychotic patients. Medications that have been used for the treatment of acute exacerbation of schizophrenia should be studied in amphetamine psychotic patients. The medications that may be of interest are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and course are also crucial for the development of study

designs appropriate for further treatment studies of amphetamine psychosis.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence of the treatment for amphetamine psychosis is limited. To our knowledge, one randomised controlled trial of treatment for amphetamine psychosis has been carried out. The results of this trial show that both olanzapine and haloperidol at clinically relevant doses can be effective in the treating patients with amphetamine psychosis. The mean doses evaluated for olanzapine and haloperidol were 7.5 mg/day and 7.8mg/day, respectively. It is important to note that these dosage levels are based on the outcomes of one trial. In the presence of equivalent clinical outcomes, however, the haloperidol condition experienced significantly more extrapyramidal side effects compared to olanzapine and outcomes from this trial suggest that in settings where cost is not a major concern, olanzapine may produce outcomes with fewer side effects. The small study sample in this report, however, makes it difficult to make this recommendation with confidence.

Although they did not meet the criteria to be included in the review, the results of two other studies in amphetamine users show that agitation and some psychotic symptoms may be abated within an hour after antipsychotic injection. Whether this limited evidence can be applied for amphetamine psychotic patients is not yet known.

Implications for research

Findings from one trial indicate use of antipsychotic medications effectively resolves symptoms of acute amphetamine psychosis. Acute psychotic symptoms frequently recur when individuals relapse to use of amphetamines. In a minority of individuals, symptoms of psychosis recur in the absence of amphetamine use. This raises significant clinical questions regarding there may be clinical benefit to continued or episode regimens of antipsychotic medications following resolution of acute amphetamine psychosis. This question is particularly important in light of the ability of the medications to resolve symptoms of psychosis, but also to cause serious side effects -- especially in the less expensive, more common, older generation antipsychotic medications. While antipsychotics are commonly used to control both agitation and psychosis symptoms, it is the case that most cases of acute amphetamine psychosis resolve in the absence of amphetamine use. There would be strong significance for a controlled trial of conventional antipsychotics, newer antipsychotics and benzodiazepines for treating acute psychosis.

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Treatment from amphetamine psychosis. *Cochrane*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Leelahanj 2005

Methods	Randomised, double-blind, 4-week study. Random allocation method not described.
Participants	58 (54 males, 4 females) who met DSM-IV criteria for amphetamine psychosis, mean age 23, mean duration of amphetamine use 4.5 yrs, mean previous psychotic episode 2.3 times. 48.2% had baseline amphetamine positive urine.
Interventions	(1) olanzapine, N = 29; (2) haloperidol, N=29. All patients started with 5-10 mg/day of the study drug. After each 7-day period, study drug could be adjusted in 5 mg increments within the allowed dose range of 5-20 mg/day during the 4 week period.
Outcomes	Clinical Global Impression, psychotic symptoms (Brief Psychiatric Rating Scale), extrapyramidal side effects (Simpson-Angus Scale and Barnes Akathisia Scale), adverse events.
Notes	Study endpoint was defined as last observation carried forward values.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baker 2006	Excluded for the type of participants not in the inclusion criteria: participant psychosis was related to mix drug use, and not specific to amphetamines.
Batki 2004	Excluded as the objective and study design were not in the inclusion criteria: not RCT, but an observational study examining the relationship between quantitative drug use levels, catecholamines, and psychotic symptoms.
Breier 1999	Excluded as the objective and study design were not in the inclusion criteria: a PET study examining the effects of risperidone and clozapine on amphetamine-induced striatal dopamine release in psychotic patients.
Brown 2003	Excluded for the type of intervention not in the inclusion criteria: participants were randomised to continue or discontinue chronic typical antipsychotic therapy.
Chen 2005	Excluded as the objective and study design were not in the inclusion criteria: an observational study examining the relationship between methamphetamine psychosis and familial loading for psychotic disorders.

Study	Reason for exclusion
Richards 1997	Excluded for the type of participants not in the inclusion criteria: participants were acutely agitated methamphetamine users, but did not necessarily have psychotic symptoms.
Srisurapanont 2003	Excluded as the objective and study design were not in the inclusion criteria: an observational cross-sectional study examining the prevalence and factors associated with methamphetamine psychosis.

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp substance-related disorders/dt,px,rh,th [Drug Therapy, Psychology, Rehabilitation, Therapy]
2. (drug or substance) adj2 (abuse* or addict* or dependen* or disorder*).ti,ab
3. withdraw*
4. 1 or 2 or 3
5. amphetamine/
6. dextroamphetamine/
7. methamphetamine/
8. (amphetamine* or methamphetamine* or dextroamphetamine*).ti,ab.
9. 4 or 5 or 6 or 7 or 8
10. psychosis, substance-induced/
11. psychosis.ti,ab
12. 10 or 11
13. randomised controlled trial.pt.
14. controlled trial.pt.
15. randomised controlled trials/
16. controlled clinical trials/
17. random\$.ti,ab.
18. Double-blind method/
19. Random allocation/
20. single blind method/
21. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp.[mp=title, abstract, registry number word, mesh subject heading]
22. clinical trial.pt.
23. clinical trials/
24. (clinical adj trial\$).ti,ab.
25. placebos /
26. placebo\$.ti,ab
27. research design/
28. exp evaluation studies/
29. follow-up studies/
30. follow up.ti,ab.
31. prospective studies/
32. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
33. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 4 and 9 and 12
35. 34 and 33
36. humans/
37. 35 not 36

Appendix 2. EMBASE search strategy

1. Substance Abuse/
2. Drug Abuse/
3. Drug Dependence Treatment/
4. (drug or substance) adj2 (abuse* or addict* or dependen* or disorder*).ti,ab
5. Withdrawal Syndrome/co, pc, dm, rh, dt, th [Complication, Prevention, Disease Management, Rehabilitation, Drug Therapy, Therapy]
6. withdraw\$.ti,ab
7. 1 or 2 or 3 or 4 or 5 or 6
8. amphetamine.ti,ab.
9. chloramphetamine.ti,ab.
- 10.methamphetamine.ti,ab.
- 11.AMPHETAMINE/ct, dt, pd, to [Clinical Trial, Drug Therapy, Pharmacology, Drug Toxicity]
- 12.Dexamphetamine/ct, ad, dt, pd, to [Clinical Trial, Drug Administration, Drug Therapy, Pharmacology, Drug Toxicity]
- 13.METHAMPHETAMINE/ct, dt, pd, to [Clinical Trial, Drug Therapy, Pharmacology, Drug Toxicity]
- 14.8 or 9 or 10 or 11 or 12 or 13
- 15.exp psychosis/
- 16.psychosis.ti,ab
- 17.15 or 16
- 18.7 and 14 and 17
- 19.Follow Up/
- 20.random\$.ti,ab
- 21.factorial\$.ti,ab
- 22.crossover\$ or cross over\$.ti,ab
- 23.placebo\$.ti,ab
- 24.doubl\$ adj blind\$
- 25.singl\$ adj blind\$
- 26.assign\$.ti,ab
- 27.allocat\$.ti,ab
- 28.volunteer\$.ti,ab
- 29.controlled trial\$.ti,ab.
- 30.Crossover Procedure/
- 31.Drug Comparison/
- 32.Double Blind Procedure/
- 33.Single Blind Procedure/
- 34.Randomised Controlled Trial/
- 35.19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
- 36.7 and 14 and 17
- 37.35 and 36

Appendix 3. CINAHL Search strategy

1. Substance Use Disorders/
2. (drug or substance) adj2 (abuse* or addict* or dependen* or disorder*).ti,ab
3. withdraw*.ti,ab
4. 1 or 2 or 3
5. amphetamines/
6. dextroamphetamine/
7. methamphetamine/
8. amphetamine.ti,ab.
9. dextroamphetamine.ti,ab.
- 10.methamphetamine.ti,ab.
- 11.5 or 6 or 7 or 8 or 9 or 10
- 12.psychosis, substance-induced/

13.psychosis
14.12 or 13
15.random*.tw..
16.clini*.tw
17.trial*.tw
18.(singl* or doubl* or tripl* or trebl*) and (mask* or blind*)
19.crossover
20.allocat*
21.assign*
22.((random* and (allocate* or assign*))
23.exp Random Assignment/
24.exp Clinical Trials/
25.15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26.4 and 11 and 14
27.26 and 25

Appendix 4. PsycInfo search strategy

1. exp Drug Abuse/
2. exp Drug Dependency/
3. exp Drug Withdrawal/
4. (drug or substance) adj2 (abuse* or addict* or dependen* or disorder*).ti,ab
5. withdraw*
6. 1 or 2 or 3 or 4 or 5
7. exp PSYCHOSIS/
8. exp AMPHETAMINE/
9. exp METHAMPHETAMINE/
10.exp Dextroamphetamine/
11.amphetamine.ti,ab.
12.chloramphetamine.ti,ab.
13.methamphetamine.ti,ab.
14.8 or 9 or 10 or 11 or 12 or 13
15.6 and 7 and 14
16.exp Clinical Trials/
17.exp Drug Therapy/
18.exp Longitudinal Studies/
19.prospective studies/
20.controlled study.mp.
21.exp Followup Studies/
22.random\$.mp.
23.controlled trial\$.mp.
24.randomised controlled trial.mp.
25.16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26.15 and 25

WHAT'S NEW

Date	Event	Description
7 August 2008	New search has been performed	updated, new search, new trial, conclusion changed
28 April 2008	New citation required and conclusions have changed	new search, new trial, conclusion changed

Date	Event	Description
23 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2001

Date	Event	Description
14 March 2008	New citation required and conclusions have changed	Substantive amendment

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Steven Shoptaw - study selection, data extraction, analysis, and writing of updated review

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DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Mental Health and Substance Dependence, World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Amphetamine-Related Disorders [*complications]; Antipsychotic Agents [*therapeutic use]; Benzodiazepines [therapeutic use]; Haloperidol [therapeutic use]; Olanzapine; Psychoses, Substance-Induced [*drug therapy]

MeSH check words

Humans